150 mg/kg of a phosphorothioate or active metabolite thereof, and wherein metastases are prevented in said animal.

A marked up copy of these amendments is attached hereto as Appendix A.

II. RESPONSE TO OFFICE ACTION

A. State of the Claims

Claims 1-31 were originally filed in this application. In response to a Restriction Requirement dated May 31, 2001, Applicants elected Group V, corresponding to claims 1-13 and 23-31. Claims 2 and 14-22 were cancelled and claims 1, 8-13 were amended in the Response filed on January 23, 2002.

Claims 1, 9-10, and 30-31 are amended herein. Support for the amended claims can be found in the claims as filed, and consequently, no new matter has been added to this application. Thus, claims 1, 3-13 and 23-33 are the subject of this response. A copy of the pending claims can be found in Appendix B.

B. The Objection under 37 C.F.R. § 1.75 Is Overcome

The Action objects to claim 1 as being a substantial duplicate of claim 30, arguing that the phrase "reducing the number of metastases" in claim 1 has the same meaning as "inhibiting metastases" in claim 30. Applicants respectfully traverse.

Applicants assert that claim 1 differs in scope from claim 30 and is not a substantial duplicate of claim 30. M.P.E.P. 706.03(k) states "court decisions have confirmed applicant's right to restate (*i.e.*, by plural claiming) the invention in a reasonable number of ways. Indeed, a mere difference in scope between claims has been held to be enough."

The term "reducing the number of metastases" in claim 1 refers to lowering the number of metastases and this meaning would be apparent to one of ordinary skill in the art. The use of this term is simply one specific way of "inhibiting metastases," which can be achieved in different ways, some of which do not involve "reducing the number of metastases." Thus, the *scope* of the claims is not the same. Accordingly, claims 1 and 30 are not duplicates and the rejection is respectfully requested to be withdrawn.

C. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

1. Claims 9 and 10 contain the requisite antecedent basis

The Action rejects claims 9 and 10 under 35 U.S.C. § 112, second paragraph, stating that there is insufficient antecedent basis for the limitation in the claims. Specifically, the Action stated that these claims recite the limitation "said derivative of aminoalkylphosporothioate" without sufficient antecedent basis for this limitation in the claims. Claims 9 and 10 have been amended to recite "said aminoalkylphosphorothioate" for which there is sufficient antecedent basis in claim 8. Accordingly, the rejection of claims 9 and 10 on this ground is overcome.

2. Claim 1 does not require an antecedent recitation

The Action rejects claim 1 under 35 U.S.C. § 112, second paragraph, stating that there is insufficient antecedent basis for the limitation in the claims. Specifically, the Action stated that these claims recite the limitation "the number of metastases" without sufficient antecedent basis for this limitation in the claims. Applicants respectfully traverse.

The Examiner is requested to consider that "the failure to provide antecedent basis does not always render the claim indefinite." *Ex parte Porter,* 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Interf. 1992). Inherent components of elements recited have antecedent basis in the recitation

of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface (MPEP 2173.05(e)).

Similarly, with the present claim an "animal with a primary tumor" is recited and reference to "the number of metastases" can be understood in that context. In the present case, taking out the article "the" or replacing it with "a" renders the claim more indefinite than leaving "the" in the claim. The standard for definiteness of a claim is whether a person of skill in the art can determine the scope of the invention based on the language of the claims with "a reasonable degree of certainty." MPEP 2173.02 (citing *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973)). A person of ordinary skill in the art would understand what the claims mean and to what " the number of metastases" refers. Accordingly, the limitation "the number of metastases" does not require an antecedent recitation and the claim fulfills the requirement of §112, second paragraph. Applicants respectfully request this rejection be withdrawn.

3. Claims 1, 3-13 and 24-31 are complete

The Action rejects claims 1, 3-13 and 24-31 under 35 U.S.C. § 112, second paragraph, stating that the claims are incomplete for omitting essential steps, which allegedly amounts to a gap between the steps. Specifically, the Action states that the omitted steps are: (i) whether the phosphorothioate or active metabolite thereof reduces the number of metastases after administration into the animal in the claims 1 and 3-13, (ii) what is the correlation of stimulation of angiostatin, stimulation of MnSOD, and the activity of metalloproteinase with reducing the number of metastases by phosphorothioate in claims 24 – 29, (iii) whether the phosphorothioate or active metabolite thereof is delivered to targeted site and inhibits metastases in an animal after administering into said animal in claim 30, and (iv) whether the phosphorothioate or active

metabolite thereof is delivered to targeted site and prevents metastases in an animal after administering into said animal in claim 30. Applicants respectfully traverse.

The Action argues that the "method is incomplete without knowing whether the phosphorothioate reach[es the] targeted site and reduces the number of metastases." Applicants contend the rationale for the rejection of claim 1 is not accurate. Claim 1 is directed to a method of reducing the number of metastases and involves "administering to said animal a subcytoprotective dose of 10 mg/kg to 150 mg/kg of a phosphorothioate or active metabolite thereof." If a person performs the recited steps of the claim, a method of reducing the number of metastases can be achieved regardless of whether the person doing those steps "know[s] whether the phosphorothioate reach[es the] targeted site and reduces the number of metastases." Stating the **effect** or **result** of the invention, as stated in the preamble, is not required to be an affirmative step. To expedite prosecution, however, Applicants have amended claim 1 to include "wherein the number of metastases is reduced." The remaining claims that are dependent upon claim 1—claims 3-13 and 24-31—are also complete and contain all the essential steps for carrying out the current invention.

The Action states that claims 24-29 are missing the essential step of the correlation between stimulation of angiostatin, stimulation of MnSOD, and stimulation of metalloproteinase with reducing the number of metastases by phosphorothioate. Applicants respectfully traverse.

A step of "correlating between stimulation of angiostatin, MnSOD, and metalloproteinase and reducing the number of metastases" is not needed the claim because a person need not perform that precise step in order to achieve the claimed invention. The correlation between stimulation of certain compounds is already disclosed in the application and/or known to those of ordinary skill in the art. The specification discloses on page 28, lines 14-15 that there exists a

positive correlation between the enhancement of angiostatin levels and a positive result with respect to achieving the claimed invention. A person simply needs to measure the stimulation in order to know what that means with respect to the claimed invention; that person does not actually "correlate" anything.

Furthermore, the specification states that inhibitors of MMP activity have been observed to be effective inhibitors of metastases formation on page 30, lines 25-26. On page 34, lines 11-12 the specification teaches that "increasing MnSOD in tumor cells causes them to loose their ability to be metastatic." The correlation is already disclosed in the specification, and therefore, again, a person performing the claimed method is not required to correlate anything to perform the method. Therefore, claims 24 – 29 are complete as claimed.

The Action further argues that claims 30 and 31 are missing the step of whether the phosphorothioate or active metabolite thereof is delivered to targeted site and inhibits (claim 30) or prevents (claim 31) metastases in an animal after administering into said animal. Applicants contend that delivery to the targeted site is not a step. Delivery to the targeted site is a result of administering the phosphorothioate or active metabolite to the animal and is not a step in the method but is the *result* of applying the steps of the invention. Applicants have demonstrated that by administering a phosphorothioate (WR-2721) to tumor-bearing mice, the probability of developing spontaneous metastases is reduced (page 24, lines 6-10). A person of ordinary skill in the art is not required to perform any intervening step; as such, the step is a superfluous recitation. Therefore, claims 30 and 31 are complete. However, in the interest of expediting prosecution Applicants have amended claim 30 to include "wherein the number of metastasis is inhibited" and claim 31 to include "and preventing metastases in said animal."

Accordingly, the rejections of claims 1, 3-13 and 24-31 on this ground are overcome.

4. *Claims 1-13 and 23-29 are not indefinite for failing to particularly point out and distinctly claim the subject matter of the invention*

The Action rejects claims 1-13 and 23-29 under 35 U.S.C. § 112, second paragraph, stating that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Action stated that the phrase "the number of metastases" in claim 1 is vague and renders the claims indefinite. The Action further states that it is unclear whether "the number of metastases" means the number of cancer cells caused by metastases or the number of tumor sites caused by metastases.

Applicants state that the phrase "the number of metastases" is not vague and is well understood to those of ordinary skill in the art. Example 2, page 27 of the specification defines metastases in stating that "[m]etastatic development results from the exfoliation of viable malignant cells from the primary tumor, their migration to distant sites followed by their invasion into normal organs and tissues and eventual growth to establish new and usually more malignant disease." Thus "the number of metastases" covers the number of cells that have migrated and metastastic tumors originating from these cells. Metastatic development results from the exfoliation of viable malignant cells from the primary tumor, their migration to distant sites followed by their invasion into normal organs and tissues, and eventual growth to establish new and usually more malignant disease as discussed in the specification on line 2, page 27 (Zetter, 1998; Ahmad *et al.*, 1997). Thus, it is clear from the application that the claim refers to a reduction in the number of metastatic developments, which refers to the number of secondary tumor sites.

Accordingly, the rejections to claims 1, 3-13 and 23-31 on this ground have been overcome.

D. Claims 1, 3-13 and 23-31 Are Enabled

The Action rejects claims 1, 3-13 and 23-31 under 35 U.S.C. § 112, first paragraph, stating that the specification does not reasonably provide enablement for inhibiting or preventing metastases by administering any phosphorothioate or active metabolite thereof, or administering WR-2721 at a concentration of 10 mg/kg to less than 50 mg/kg to an animal. The Action further states that the specification does not enable any person skilled in the art to use the invention commensurate in scope with these claims. However, it acknowledges that the specification is enabling for inhibiting or preventing metastases by administering WR-2721 at a concentration of 50 mg/kg to 150 mg/kg to an animal.

The Action further states that phosphorothioate compounds encompass any compound that has phosphors and thio-group and the genus of the compound is very broad and that the prior art also only teaches using amifostine and c-myc antisense phosphorothioate oligonucleotide for protection against metastases.

The Action then states that the specification fails to provide adequate guidance and evidence for inhibition and prevention of metastases of various tumors as well as various tumors *in vivo* using any phosphorothioate and active metabolites thereof other than WR-2721 and cites Kanclerz as well as Milas for support. The Action contends that one skilled in the arts would have to perform undue experimentation to practice the full scope of the invention claimed.

Applicants respectfully traverse.

1. *Invention is operable as disclosed in the specification*

The Action contends that the claims are very broad and that they are not enabled for the scope of the invention. This is incorrect with respect to both statements.

The claims are not as broad as the Action contends. The Action states that the claims cover any "phosphorothioate compounds encompass any compound that has phosphors and thio-group." This is incorrect. The term "phosphorothioates" does not refer to *any compound* that has phosphors and a thio group. It refers to a discrete chemical make-up, and thus, Applicants request that the Examiner provide a reference to support their proposition because this is contrary to the understanding conveyed not only by the present application but also by the numerous patents issued by the PTO that describe or claim "phosphorothioates."

Furthermore the Examiner has not provided any reasonable explanation for why phosphorothioates and its active metabolites is a very broad genus or for the relevance of the prior art's teaching the use of amifostine and c-myc antisense phosphorothioate oligonucleotide for protection against metastases. There is no reason to doubt that the invention is not operable as disclosed in the specification.

The burden is on the examiner under the enablement requirement to provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure (MPEP 2164.04). Applicants contend that the examiner has provided no reasonable explanation as to why the scope of protection provided by claims 1, 3-13 and 23-31 is not adequately enabled by the disclosure.

Accordingly, the scope of the claim is not so broad that the teaching of the specification does not fulfill the requirements of § 112, first paragraph. Applicants contend that claims 1, 3-13 and 23-31 are enabled under 35 U.S.C § 112, first paragraph.

2. *The specification provides adequate guidance and evidence for the inhibition and prevention of metastases of various types of tumors.*

The Action also contends that the claims are not enabled with respect to working with any type of tumor. It cites Kanclerz *et al.*, 1988 ("Kanclerz") in which the radioprotector WR-

2721, when given at 400 mg/kg, resulted in the promotion of lung metastases. This reference is not relevant to the enablement of claims 1, 3-13 and 23-31 because these claims are directed at a subcytoprotective therapy, which is not at all addressed by the Kanclerz reference. Instead, Kanclerz discusses radiotherapy, which is a different therapy than subcytoprotection.

The Action also cites Milas *et al.* ("Milas") as reporting about the degree of tumor radioprotection afforded by WR-2721. Again, this reference is irrelevant to the claimed invention. Both Kanclerz and Milas refer to the use of WR-2721 as a **radioprotector** to provide protection to cells **during exposure to radiation** therapy. The current invention is focused on a subcytoprotective dose of a phosphorothioate or active metabolite thereof and is thus distinguishable over the cited references. As discussed in the specification, "subcytoprotection" refers to an amount "that is **too low** to prevent cell killing and/or loss of function in normal tissues exposed to radiation and chemotherapy." Specification at page 6 (emphasis added). Radioprotection, on the other had, is simply the protection of normal cells exposed to radiation. Therefore, what these references say about the radioprotection effect on tumors bears no significance about the subcytoprotective effect on tumors.

The examiner has provided no reference to support the assertion that the two therapies are interchangeable. The court in *Gould v. Mossinghoff*, 229 USPQ 1 (D.C. 1985) stated:

> In examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-370 (CCPA. 1971).
>
> The PTO thus must provide reasons supported by the record as a whole what the specification is not enabling. *Application of Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219-220 (CCPA 1979). Then and only then does the burden shift to the applicant to show that one of ordinary skill in the art could have practiced the claimed invention without undue experimentation. *In re Strahilevitz*, 668 F.2d. 1229, 1232, 212 USPQ 561, 563-64 (CCPA 1982) (emphasis added).

The PTO has not shifted the burden in this case because the cited references are irrelevant with respect to the claimed invention. If the examiner would like to maintain this position, Applicants request a reference or affidavit to support this contention, as required by MPEP § 2144.03.

Applicants contend that there is no reason to believe the invention is not operable with respect to different tumors. As argued in a previous response, data is provided in the specification with respect to different tumor cells. Tumor systems with different growth rates including the sarcoma SA-NH, the adenocarcinomas Mca-K and Oca-I were studied. Specification at page 25.

There is no reason to believe the claims are not enabled. Accordingly, Applicants respectfully request this rejection be withdrawn.

3. ***The specification provides adequate guidance and evidence for the inhibition and prevention of metastases in vivo.***

The Action contends that the specification fails to provide adequate guidance with respect to *in vivo* application of the claimed invention. Applicants point to the specification where the effectiveness of phosphorothioates on multiple tumor systems is shown on pages 24-25. As discussed earlier, the effectiveness of the current invention against various tumors has been established. Furthermore, Tables 1 and 2 on page 25 demonstrate the effectiveness of a single dose of 50 mg/kg of WR-2721 for various tumor types (SA-NH, Mca-K, and Oca-I). Similarly, dosage schedules of 50-100 mg/kg every other day for 6 days (page 28, line 9) and a dose 50 mg/kg every third day (pg. 23, line 18) are demonstrated. Therefore, both single dosage and multiple dose schedules are used in the current invention.

Again, the Action cites the Kanclerz reference, which the Applicants have already argued is not relevant with respect to the claimed invention. Kanclerz says nothing about subcytoprotection.

Moreover, the specification provides *in vivo* data. On page 23-24, tumors were assayed in mice and the results of those experiments are disclosed and shown in FIGs. 1 and 2. The demonstration of treatment in mice is adequate enablement of the claimed invention; proof of efficacy in clinical trials involving humans is not a requirement for patentability. *See In re Brana,* 51 F.3d 1560 (Fed. Cir. 1995). *See also Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Title 35 does not demand that such human testing occur within the confines of Patent and Trademark (PTO) proceedings.").

The claims are enabled for *in vivo* use. The Applicants have taught such use in their specification. Also, the reference cited by the examiner is again not relevant. Applicants submit that the rejections of claims 1, 3-13 and 23-31 under 35 U.S.C. § 112 are overcome.

E. The Rejections Under 35 U.S.C. § 103 Are Overcome

1. Claims 1, 3-13, 30, and 31 are not obvious over Milas in view of Kanclerz

The Action rejects claims 1, 3-13, 30 and 31 under 35 U.S.C. § 103(a) as being unpatentable over Milas *et al.*, (1984) ("Milas"), in view of Kanclerz *et al.*, (1988) ("Kanclerz"). Specifically the Action argues that Milas teaches that amifostine (WR-2721) can greatly reduce the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice that had been injected i.v. with fibrosarcoma. The Action alleges that WR-2721 was given intraperitoneally at a dose of 400 mg/kg and was capable of significant protection against metastases enhancement induced by CY and WBI. The Action further alleges that

Kanclerz teaches that treatment with a single dose (400 mg/kg) of WR-2721 promoted lung metastases but exerted a suppressive effect on lymph node tumors; when the radioprotector was given in three different doses (50 mg/kg, 100 mg/kg and 200 mg/kg), a slight enhancement of lung metastases and suppression of extrapulmonary metastases was observed. The Action then argues that it would have been obvious for one of ordinary skill in the art to use WR-2721 in the range of 50 mg/kg to 200 mg/kg to suppress extrapulmonary metastases.

To establish a *prima facie* case of obviousness, under 35 U.S.C. § 103, three basic criteria must be met: (1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2142. *See also In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure).

In response to the above rejections Applicants submit that a proper *prima facie* case has not been made and provide the following replies to the rejections.

a. Kanclerz reference is not enabling and is not proper prior art

For a reference to anticipate or render obvious a claimed invention, it must be enabling. MPEP § 2121.01. According to the MPEP, a "reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention." *Id.*; *see also Ex Parte Gould*, 231 U.S.P.Q. 943 (B.P.A.I.). The Court of Appeals for the Federal Circuit has stated, "Such possession is effected if one of ordinary skill in the art could have combined the

publication's description of the invention with his [or her] own knowledge to make the claimed invention." *Id.* (citing *In re Donohue*, 766 F.2d 531, 226 U.S.P.Q. 619 (Fed. Cir. 1985).

The Kanclerz reference is not enabling, and accordingly, it is not a proper prior art reference. While the Kanclerz reference states "suppression of extrapulmonary metastases was observed," the experimental evidence to support this statement is tenuous. Extrapulmonary tissue was simply *weighed* after treatment and compared to tissue in mice that had not been treated. This does not show that the treatment caused suppression of metastases, particularly because compounds such as WR-2721 are well known to delay the growth of cells, whether cancerous or not. That the authors observed a lower weight for the treated tissue when compared to the untreated tissue is consistent with WR-2721 being a general cell growth inhibitor. Thus, a person of ordinary skill in the art would not consider the Kanclerz reference to have placed the invention in the public because it does not prove that suppression of metastases was achieved.

Further, this reference is not enabled with respect to the claimed invention. Claim 1 recites, "A method of reducing the number of metastases in an animal...." Based on the Kanclerz reference, it cannot be determined whether the number of metastases is reduced or whether metastases are inhibited because no investigation of metastases specifically was undertaken. The Kanclerz reference provides insufficient evidence that would permit one of skill in the art to ascertain whether or not the limitations of the claims are addressed. It is not enough for the reference to cite merely the words of the claimed invention without an accompanying enabling disclosure. Therefore, the Kanclerz does not show that invention claimed in the present application would work.

Furthermore, Kanclerz asserts that reduction of tissue weight is directly proportional to the amount of amifostine drug administered. However, a review of Figure 4 shows that the dose

of 0.05 g/kg is not significantly different from the untreated control organ weights. In two out of the four organ endpoints used, only the 2 g/kg dose is significantly different from the control values. This closer scrutiny of the data further confirms that the cited reference does not teach the claimed invention.

This is in contrast to the present specification. The specification, for example at page 24, lines 1-4, provides data about metastases by measuring both the number of metastases following treatment and evaluates the incidence of metastases (whether metastases occurs at all). The specification provides additional information to show that phosphorothioates effect reduction in the number of metastases and inhibit metastases.

Therefore, the Kanclerz reference is not sufficiently enabled to be a proper prior art reference.

b. There is no suggestion or motivation to combine references

With regard to Kanclerz, a valid *prima facie* case of obviousness has not been made because "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." MPEP 706.02(j). *See also In re Fine*, 837 F.2d at 1074; *In re Jones*, 958 F.2d at 351. The Action contends that a person of ordinary skill in the art would combine the dosages in Kanclerz, which allegedly teaches the use of 0.05 g/kg, 0.1 g/kg and 0.2 g/kg of WR-2721 as a radioprotector, for inhibiting metastases or preventing metastases, with Milas *et al.*, which teaches that WR-2721 when given intraperitoneal (i.p.) as a radioprotector at a dose of 400 mg/kg results in spontaneous metastases in mice.

However, both Kanclerz and Milas teach the use of WR-2721 as a **radioprotector** used in radiotherapy to protect normal cells from being harmed by the radiation. These references

teach a different therapy with respect to the claimed invention, and as such, there is no suggestion or motivation to combine these references to achieve the claimed invention.

Furthermore, the results of Kanclerz are *ambiguous* in that the dosage range cited, 0.05g/kg, 0.1g/kg and 0.2g/kg, could result in an enhancement or suppression of metastases, which is precisely the opposite result of the claimed invention. In other words, the cited reference actually *teaches away* from the claimed invention. The claimed invention would produce unacceptable results, a rejection based on it is "the very antithesis of obviousness." *In re Buehler,* 185 U.S.P.Q. 781, 787 (C.C.P.A. 1975).

Accordingly, there is no motivation or suggestion in Kanclerz that would lead one of ordinary skill in the art to combine the dosage range, 0.05g/kg, 0.1g/kg and 0.2g/kg, with Milas, which teaches that WR-2721 as a radioprotector greatly reduces spontaneous metastases in mice, or vice versa.

c. No reasonable expectation of success

To establish a valid *prima facie* case of obviousness under, 35 U.S.C. § 103(a), there must also be a reasonable expectation of success and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (MPEP 706.02(j)).

Because Kanclerz teaches that WR-2721 is a radioprotector and Milas similarly is related to radioprotection, a person of skill in the art would not have a reasonable expectation of success of inhibiting or reducing metastases according to the steps of the invention. One would not know to use a subcytoprotective dose of phosphorothioates or active metabolites to achieve the claimed invention.

Furthermore Kanclerz teaches that WR-2721 promotes lung metastases as well as inhibited extrapulmonary metastases. Without extensive experimentation—such as those

described in the specification—a person of skill in the art would not know he could achieve the claimed invention.

Applicants submit that the rejections of claims 1, 3-13, 30, and 31 under 35 U.S.C. § 103(a) are overcome.

2. *Claims 1, 23, and 25-29 are not obvious over Milas et al., 1984 (IDS-C51) in view of Kanclerz and further in view of Golub (U.S. Patent No. 5,837,696) and Antras-Ferry et al., (1997)*

The Action rejects claims 1, 23, and 25-29 as being obvious over Milas in view of Kanclerz and further in view of Golub (U.S. Patent No. 5,837,696) ("Golub") and Antras-Ferry *et al.*, (1997) ("Antras-Ferry"). The Action argues that Golub teaches that MMP expression, especially gelatinase expression, is associated with cancer invasiveness or metastasis, and suggests detection of MMP gene products for a prophylactic treatment using tetracycline compound. Based on this teaching, the Action states that it would be obvious for one of ordinary skill in the art at the time of the invention to monitor the ability of the phosphorothioate to reduce metastasis by measuring the stimulation of MnSOD gene expression because Golub suggests the monitoring methods can be used as a prophylactic treatment by administering the tetracycline compound after detection of a gene product or metabolite associated with predisposition to a cancer. In response to the above rejections Applicants submit that a proper *prima facie* case has not been made and provide the following replies.

a. There is no suggestion or motivation to combine references

As discussed earlier, there is no motivation to combine Milas and Kanclerz for the reasons previously outlined. Accordingly, there is no reason for one of skill in the art to combine Milas and Kanclerz with Golub and Antras-Ferry since the results of Kanclerz and Milas teaches a radioprotective therapy which is different from the current invention as outlined previously.

Furthermore, Golub and Antras-Ferry teach methods of inhibiting cancer growth by administering a cancer-inhibitory dose of a tetracycline compound, CMT-3, and Oltipraz respectively, but neither mentions or suggest administering a phosphorothioate at a subcytoprotective dose for reducing the number of metastases in an animal. Thus, the teachings of Golub or Antras-Ferry would not suggest or motivate one of skill in the art to combine them to make obvious the present invention.

Golub also teaches that metalloproteinase expression, (MMP), MMP-2 and MMP-9, is associated with cancer invasiveness or metastasis and that CMT-3 inhibits the expression of MMP-2 and MMP-9 in cancer cells *in vitro.* Antras-Ferry also teaches that Oltipraz induces the transcription of the manganese superoxide dismutase (MnSOD) in a dose-dependent manner. However, there is no motivation or suggestion for one of ordinary skill in the art to monitor changes in MnSOD, MMP, MMP-2 or MMP-9 levels after administration of a phosphorothioate and not any other compound.

Applicants submit that the rejections of claims 1, 23 and 25-29 under 35 U.S.C. § 103(a) are overcome.

3. Claims 1, 23, and 24 are not obvious over Milas in view of Kanclerz and further in view of Gately et al., 1997

The Action rejects claims 1, 23, and 24 as being obvious in view of Kanclerz and further in view of Gately et al., 1997 (IDS-C13) ("Gately"). The Action argues that Gately teaches angiostatin inhibits angiogenesis *in vitro* and *in vivo* and suppresses the growth of Lewis lung carcinoma metastases and that it would have been obvious for one of ordinary skill in the art at the time of the invention to measure the stimulation of angiostatin to monitor the ability of the

subcytoprotective dose of phosphorothioate or active metabolite thereof to reduce metastases in an animal.

In response to the above objections Applicants submit that a proper *prima facie* case has not been made and provide the following replies to the rejections.

a. There is no suggestion or motivation to combine references

As discussed earlier there is no motivation to combine Milas and Kanclerz for the reasons previously outlined. Accordingly, there is no reason for one of skill in the art to combine Milas and Kanclerz with Gately since the results of Kanclerz and Milas teaches a radioprotective therapy which is different from the current invention as outlined previously. Accordingly, there is no suggestion or motivation to combine Milas, Kanclerz and Gately to arrive at the present invention.

Furthermore, there is no reason to combine Milas and Kanclerz with Gately since Gately teaches that angiostatin inhibits angiogenesis and suppresses the growth of Lewis lung carcinoma metastases, but does not mention a phosphorothioate or a subcytoprotective dose. The Action argues that stimulation of angiostatin would indicate the reduction of metastases. However, there is no motivation or suggestion for one of skill in the art to monitor angiostatin stimulation after administration of a phosphorothioate and not any other compound. Accordingly, there is no suggestion or motivation to combine Milas, Kanclerz and Gately to arrive at the present invention.

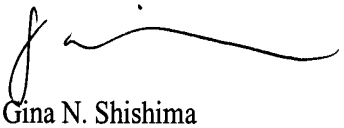
Applicants submit that the rejections of claims 1, 23 and 24 under 35 U.S.C. § 103(a) are overcome.

CONCLUSION

It is submitted that in light of the foregoing remarks, the invention embraced by the pending claims has been shown to be patentable, and favorable reconsideration is earnestly solicited.

The Examiner is invited to contact the undersigned attorney at 512-536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: October 1, 2002

APPENDIX A
Claim Amendments

1. (Twice Amended) A method for reducing the number of metastases in an animal exhibiting a primary tumor comprising administering to said animal a subcytoprotective dose from 10 mg/kg to 150 mg/kg of a phosphorothioate or active metabolite thereof, wherein the number of metastases is reduced.

9. (Twice Amended) The method claim 8, wherein said [active derivative of] aminoalkylphosphorothioate is the thiol form.

10. (Twice Amended) The method claim 8, wherein said [active derivative of] aminoalkylphosphorothioate is the disulfide form.

30. (Twice Amended) A method for inhibiting metastasis in an animal exhibiting a primary tumor comprising administering to said animal a subcytoprotective dose of 10 mg/kg to 150 mg/kg of a phosphorothioate or active metabolite thereof, wherein the number of metastases is inhibited.

31. (Twice Amended) A method for preventing metastasis in an animal exhibiting a primary tumor comprising administering to said animal a subcytoprotective dose of 10 mg/kg to 150 mg/kg of a phosphorothioate or active metabolite thereof, and wherein metastases are prevented in said animal.

APPENDIX B
Unofficial Copy Of Claims Currently Pending

1. A method for reducing the number of metastases in an animal exhibiting a primary tumor comprising administering to said animal a subcytoprotective dose of 10 mg/kg to 150 mg/kg of a phosphorothioate or active metabolite thereof, wherein the number of metastases is reduced.

3. The method of claim 1, wherein the dose is about 10 mg/kg to about 100 mg/kg.

4. The method of claim 1, wherein the dose is about 10 mg/kg to about 50 mg/kg.

5. The method of claim 1, wherein the dose is about 10 mg/kg to about 25 mg/kg.

6. The method of claim 1, wherein said animal is a human.

7. The method of claim 1, wherein said tumor is a sarcoma or carcinoma.

8. The method of claim 1, wherein said phosphorothioate is an aminoalkylphosphorothioate compound.

9. The method claim 8, wherein said aminoalkylphosphorothioate is the thiol form.

10. The method claim 8, wherein said aminoalkylphosphorothioate is the disulfide form.

11. The method of claim 1, wherein said phosphorothioate or active metabolite thereof is selected from the group consisting of WR-2721 (amifostine), WR-1065, WR-638, WR-77913, WR-33278, WR-3689, WR-2822, WR-2529, WR-255591, WR-2823, WR-255709, WR-151326 and WR-151327.

12. The method of claim 1, wherein the route of administration of said phosphorothioate or active metabolite thereof is intravenous, intraperitoneal, intradermal, intramusculara l, dermal, nasal, buccal, rectal, vaginal, inhalation, or topical.

13. The method of claim 1, wherein said phosphorothioate or active metabolite thereof is formulated into solutions, suspensions, tablets, pills, capsules, sustained release formulations, powders, creams, ointments, salves, sprays, pumps, liposomes, suppositories, inhalers, and patches.

23. The method of claim 1, further comprising monitoring the ability of the subcytoprotective dose of a phosphorothioate or active metabolite to reduce metastases in the animal.

24. The method of claim 23, wherein the monitoring comprises measuring the level of angiostatin stimulation.

25. The method of claim 23, wherein the monitoring comprises measuring the level of activity of a matrix metalloproteinase.

26. The method of claim 25, wherein the matrix metalloproteinase is MMP-2.

27. The method of claim 25, wherein the matrix metalloproteinase is MMP-9.

28. The method of claim 23, wherein the monitoring comprising measuring the stimulation of MnSOD.

29. The method of claim 28, wherein the measuring of MnSOD stimulation comprises measuring the stimulation of MnSOD gene expression.

30. A method for inhibiting metastasis in an animal exhibiting a primary tumor comprising administering to said animal a subcytoprotective dose of 10 mg/kg to 150 mg/kg of a

phosphorothioate or active metabolite thereof, wherein the number of metastases is inhibited.

31. A method for preventing metastasis in an animal exhibiting a primary tumor comprising administering to said animal a subcytoprotective dose of 10 mg/kg to 150 mg/kg of a phosphorothioate or active metabolite thereof, and wherein metastases are prevented in said animal.

32. The method of claim 11, wherein said phosphorothioate or active metabolite thereof is WR-2721.

33. The method of claim 11, wherein said phosphorothioate or active metabolite thereof is WR-1065.